

Diabetes and periodontal disease: What should we learn next?

Both diabetes and periodontal disease are highly prevalent worldwide, and the prevalence is higher in the aged population. Epidemiological studies have shown a link between periodontal disease and diabetes for nearly a century (Figure 1). In 1936, Sheppard¹ first noted a higher incidence of periodontitis in diabetic patients. It is now widely accepted that periodontal disease is one of the diabetic complications. In addition, many epidemiological studies have shown a bidirectional relationship between periodontal disease and diabetes.

Bacterial biofilm (also known as dental plaque) forms on the surfaces of teeth, and chronic microbial stimulation induces local inflammation in the gingival tissues, which is termed gingivitis. Gingivitis is reversible by appropriate oral hygiene and mechanical disruption of the biofilm. However, long-term plaque accumulation induces sustained inflammation and the destruction of periodontal tissues, such as the formation of periodontal pockets, loss of connective tissue attachment and loss of alveolar bone, which is termed periodontitis. If periodontitis is left untreated, tooth loss can occur. Periodontal disease includes gingivitis and periodontitis.

It is accepted that periodontal disease is more prevalent and more severe in persons with type 1 and type 2 diabetes than in non-diabetic persons. A German population-based longitudinal study showed that uncontrolled (glycated hemoglobin $\geq 7.0\%$) type 1 or type 2 diabetes is associated with the progression of periodontal disease². Although the mechanisms by which hyperglycemia induces periodontal destruction have yet to be fully elucidated, the biological plausibility is based on diabetes-related features, such as inflammatory response abnormalities,

vascular abnormalities, the uncoupling of bone destruction/repair and the effects of metabolic disorders. The receptor of advanced glycation end-products (AGEs) expression was found to be increased in the gingival tissues of individuals with diabetes mellitus and periodontitis. Increased AGE formation is involved in the pathogenesis of diabetic complications. Several studies, not so much as AGE, showed the involvement of other factors, such as the activation of protein kinase C, polyol pathway and oxidative stress in periodontitis in diabetic animals. Taken together, diabetic complications and the progression of periodontal disease under the diabetic condition might share a common pathogenesis. In contrast, it has been reported that the subgingival bacterial profiles were not different between diabetic patients and non-diabetic subjects, suggesting that it is not the bacterial profiles, but the host response that is responsible for the progression of periodontal disease in diabetic patients. Further studies are required in this field.

A systematic review reported that type 2 diabetes mellitus patients with poorer periodontal health have a greater risk of developing poorer glycemic control³. Randomized prospective studies were carried out mainly during the past two decades. Meta-analysis showed that the treatment of periodontal disease can reduce the glycated hemoglobin level on average by 0.40% in type 2 diabetes patients⁴. However, the number of patients was small, and the treatment of periodontal disease varied among the studies used in this meta-analysis. Recent the Diabetes and Periodontal Therapy Trial (DPTT), a large-scale multicenter randomized clinical trial, showed that non-surgical periodontal therapy did not improve glycemic control in type 2 diabetes patients despite the improvement of the periodontal measurements⁵. The treatment of periodontal disease of DPTT is restricted by scaling and root planing plus chlorhexidine oral rinse at baseline, and supportive periodontal therapy. In contrast, many of the previous small-scale prospective studies included surgical therapy or the use of antibacterium. Further large-scale study is necessary to provide clinical evidence of whether treatment of periodontal disease ameliorates glycemic profiles and which treatment of periodontal disease is favorable for diabetic patients.

Does periodontal disease affect diabetic complications? A prospective study of 628 Pima Indians with type 2 diabetes mellitus, the median follow up of which was 11 years, showed a significant increase of the adjusted relative risk for cardio-renal mortality in those with severe periodontitis (odds ratio 3.2) compared with those with no or only mild to moderate periodontitis⁶. In 2012, the American Heart Association⁷ reviewed the relationship between periodontal disease and atherosclerotic vascular disease in their scientific statement. They reported that epidemiological

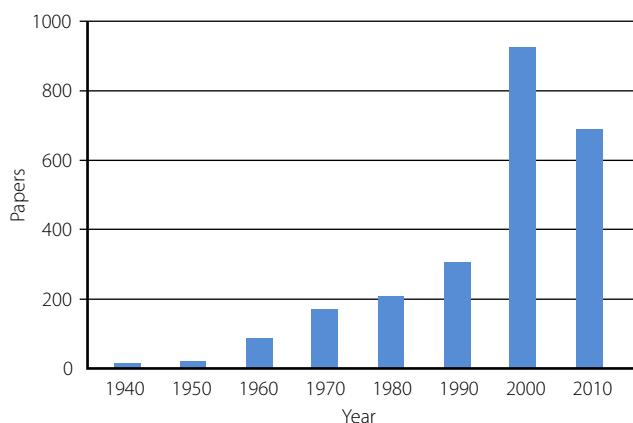


Figure 1 | The number of papers about periodontal disease and diabetes in PubMed.

and experimental studies showed an association between periodontal disease and atherosclerotic vascular disease. However, they also reported the lack of evidence that treatment of periodontal disease would prevent atherosclerotic vascular disease or modify its outcome. Vascular abnormalities, both macrovascular and microvascular, are characteristic diabetic complications. The relationship between microvascular/macrovascular diabetic complications and periodontal disease might have some similarities with that between cardiovascular disease and periodontal disease. So far, there have been only a small number of studies about the relationship between diabetic macrovascular/microvascular complications and periodontal disease. Further large-scale clinical studies and pathological animal studies are required.

The relationship between diabetes and Alzheimer's disease has been vigorously discussed, and chronic inflammation is considered as one of the key factors connecting these diseases. The relationship between the oral disease and dementia is also of interest. A prospective cohort study based on the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial showed that tooth loss was associated with the risk of dementia and cognitive decline in type 2 diabetes patients⁸. Although the oral condition of that study was only assessed by two questions, the results might suggest the possible involvement of periodontal disease in dementia of diabetes patients.

As aforementioned, periodontal disease is accepted as one of the diabetic complications by its high prevalence and severity in diabetes patients. Additionally, there is a bidirectional relationship between periodontal disease and diabetes. A recent consensus report of the Joint European Federation of Periodontology and the American Academy of Periodontology (EEP/AA) workshop on periodontitis and systemic disease also discussed a strong relationship between periodontal disease and diabetes⁹. However, large-scale randomized prospective trials and pathological studies including animal studies are required for further investigation.

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